REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1, 2, 4, 8, 11, and 38, the only claims pending and under examination in this application after consideration of the comments below.

The Applicants would like to thank the Examiner for acknowledging that Claim 11 includes allowable subject matter. Accordingly, Claim 11 has been amended so as to be in independent format. Claim 11, therefore, has been amended to incorporate the limitations of Claims 1 and 4, the base claims from which Claim 11 previously depended. Consequently, Claim 11 is allowable, which notice thereof the Applicants respectfully request.

Claim 1 has been amended to clarify the claim language. Specifically, Claim 1 has been amended to clarify that the linker moiety is a "self-immolating" linker moiety. Support for this amendment is found throughout the specification and claims as originally filed. For instance, support may be found at Claim 1 as originally filed. Additionally, Claim 1 has been amended to retain only the species of transporter moiety under examination in the present case.

Accordingly, no new matter has been added by way of these amendments and their entry is respectfully requested.

Election/Restriction

The Office has withdrawn previously entered Claim 38 as being drawn to a non-elected invention. Specifically, the Office contends that the invention set forth in Claim 38 does not further limit the invention. The Applicants respectfully disagree. Claim 1 is drawn to a biologically active compound that includes a transport moiety and a self –immolating linker moiety linking the biologically active compound and the transport moiety. Claim 38 limits Claim 1 in that Claim 38 recites that the linker moiety comprises a half-life in the range of between about 10 minutes and about 24

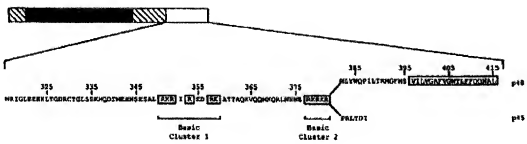
hours in water at 37 °C and at a pH of approximately 7.4. As these elements are not recited in Claim 1, they do in fact limit Claim 1 by reciting further claim limitations with respect thereto. Accordingly, the Applicants contend the withdrawal of Claim 38 by the Office is in error, and the Applicants respectfully request that this claim be rejoined.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 2 and 8 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Lorenzen, et al., Journal of Cell Biology, 1995, 131:631-643 ("Lorenzen").

Claim 1 is directed to a composition that includes a biologically active compound, a transport moiety comprising a structure of $(ZY)_nZ$, and a self-immolating linker moiety which linker moiety links the biologically active compound and the transport moiety.

The Office asserts that Lorenzen anticipates the Applicants' claimed invention because Lorenzen discloses the following construct:



Specifically, the Office asserts that in the above construct a catalytic region in black is equated with the Applicants' claimed biologically active moiety; a nuclear localization signal region, represented in part by the RKRKR basic cluster, is equated with the Applicants' claimed transport moiety; and an intervening sequence of amino acids is equated with the Applicants' claimed linker moiety.

Applicant respectfully traverses the rejection as Lorenzen does not disclose the composition of claim 1. Lorenzen does not disclose a self-immolating linker moiety.

The specification of the present invention refers to "self-immolating" at para 0060:

> Such [self-immolating] linking moieties in a transport moiety-biologically active compound conjugate contain a nucleophile (e.g., oxygen, nitrogen, and sulfur) distal to the biologically active compound and a cleavable group (e.g. ester, carbonate, carbamate, and thiocarbamate) proximal to the biologically active compound. Intramolecular attack of the nucleophile on the cleavable group results in the scission of a covalent bond, thereby releasing the linking moiety from the biologically active compound.

Lorenzen did not disclose a self-immolating linker moiety as provided by claim 1. In fact, the protein of Lorenzen is intact *in-vivo*, as the $p48^{TC}$ form of TCPTP was isolated from human peripheral T cells as the full length protein, including the region that the Examiner alleges to contain a self-immolating linker moiety. See Lorenzen, page 631, column 1, lines 19-22.

If in fact the protein as represented in Figure 1 did contain a self-immolating linker moiety and transporter of claim 1, as asserted by the Office, the isolated protein of Figure 1 would not contain at least amino acid residues 377 and onward. The entire sequence of TCPTP, including residues R377, K378, R379, K380 and R381, was isolated, which indicates that the protein of Lorenzen did not contain a self-immolating linker moiety.

Consequently, the Applicants contend that Lorenzen does not teach all of the elements of the rejected claims, a self-immolating linker moiety linking the biologically active compound and the transport moiety. Therefore, because Lorenzen does not teach all the elements of the rejected claims it fails to anticipate the claimed invention, in view of which, the Applicants respectfully request that the rejection of independent Claim 1, and claims 2, 4, 8, and 38 dependent upon it, be withdrawn.

Claims 1 and 4 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Olsson et al., Biochim. Biophys. Acta, 1991, 1097:37-44 ("Olsson").

The Office asserts that Olsson anticipates the Applicants' claims because the claims do not preclude the presence of other compounds that could assist in the cleavage of the peptide fragment RSRSRSRSRSR from its association with LDL and chondroitin 6-sulphate.

Applicants respectfully traverse the rejection as Olsson does not disclose a composition of claim 1, which contains a self-immolating linker moiety. A "self immolating linker moiety" as provided in claim 1 and discussed above, is covalently bonded to the biologically active compound and the transport moiety. The complex of peptide RSRSRSRSRSR and chondroitin-6-sulfate of Olsson was not covalently bonded.

Based on the foregoing, the Applicants contend that Olsson does not teach all of the elements of the rejected claims, namely, a self-immolating linker moiety linking the biologically active compound and the transport moiety. Consequently, because Olsson does not teach all the elements of the rejected claims it fails to anticipate the claimed invention. The Applicants, therefore, respectfully request that this rejection of independent Claim 1, and claims 2, 4, 8, and 38 dependent upon it, be withdrawn.

Claims 1, 2, 4, and 8 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Mixson, US Patent No. 7,070,807 ("Mixson").

The Office asserts that Mixson anticipates the Applicants' claims because Mixson discloses the use of a liposome for the intracellular delivery of a transport polymer that is in association with the transport polymer. Specifically, the Office asserts that Mixson discloses a polymer: liposome: DNA complex wherein the liposome functions as a linker linking the polymer and the DNA.

Applicants respectfully traverse the rejection as Mixson did not disclose a composition of claim 1, comprising a self-immolating linker moiety.

Mixson disclosed an arginine-histidine copolymer (SEQ ID 13). Mixson disclosed that the transport polymer and the pharmaceutical agent may be covalently bonded. See Mixson, col. 15, lines 32-34. However, the only covalent attachments disclosed in Mixson were:

Such covalent attachment may be direct, for example through a -

> COOH group(s) of the polymer with an –NH2 or –OH group of the pharmaceutical agent or the reverse. Alternatively the pharmaceutical agent may be attached to the transport polymer using a coupling agent such as di-carboiimide [sic]. See Mixson, col. 15, lines 35-40.

If the covalent attachment was "direct" as defined by Mixson, the only residue which was directly attached to the pharmaceutical agent was arginine. The side chain of arginine does not have a nucleophile as discussed above for a "self-immolating linking moiety" as it has a guanidinium group, not an amine. The pKa of the guanidinium group of arginine is 12.48. Under in-vivo or in-vitro conditions capable of sustaining live cells, the guanidinium group is protonated and is not a nucleophile, and hence is not a self-immolating linker moiety as provided by claim 1.

Alternatively, if the covalent attachment is not direct, the only coupling agent which was disclosed by Mixson was carbodiimide. Thus the only possible intramolecular cleavage possible was via nucleophilic attack of the side chain guanidinium group of arginine. As discussed above, the guanidinium group in the side chain of arginine is not a nucleophile at physiologically relevant pH, and therefore the guanidinium group cannot comprise a self-immolating linker moiety for indirect covalent attachment as disclosed by Mixson.

Based on the foregoing, Mixson does not teach all of the elements of the rejected claims, namely, a self-immolating linker moiety linking the biologically active compound and the transport moiety. Consequently, because Mixson does not teach all the elements of the rejected claim, it fails to anticipate the claimed invention. The Applicants, therefore, respectfully request that that this rejection of independent Claim 1, and claims 2, 4, 8, and 38 dependent upon it, be withdrawn.

CONCLUSION

In view of the amendments and remarks above, Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Respectfully submitted,

By: _____

James S. Nolan
Registration No. 53,393
c/o MINTZ LEVIN
1400 Page Mill Road
Palo Alto, California 94304-1124
(650) 251-7700 Telephone
(650) 251-7739 Facsimile
Customer Number 23980

4333953v.1